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Health and Environmental
Effects Profile for Hexamethylenediamine

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR HEXAMETHYLENEDIAMINE

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16. ABSTRACT The Health and Environmental Effects Profile for <u>hexamethylenediamine</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for <u>hexamethylenediamine</u>. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.		
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA and CERCLA dockets.

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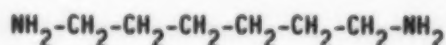
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
bw	Body Weight
COD	Chemical oxygen demand
DNA	Deoxyribonucleic acid
GI	Gastrointestinal
HCG	Human chorionic gonadotrophin
i.p.	Intraperitoneal
i.v.	Intravenous
LD ₅₀	Dose lethal to 50% of recipients
OECD	Organization for Economic Cooperation and Development
ppm	Parts per million
RNA	Ribonucleic acid
TS	Total solids

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Hexamethylenediamine has the following synonyms: 1,6-diaminohexane; 1,6-hexanediamine; 1,6-hexylenediamine; and HMDA. The structure and molecular formula are as follows:



Molecular weight: 116.21

Molecular formula: $\text{C}_6\text{H}_{16}\text{N}_2$

The Chemical Abstract Service (CAS) Registry number is 124-09-4.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Hexamethylenediamine appears as colorless leaflets at room temperatures (Verschueren, 1983). It is soluble in alcohol, ether and benzene. Available physical properties are listed below:

Melting point:	40.9°C	Spitz, 1979
Boiling point:	204.5°C	Spitz, 1979
Specific gravity:	0.889-0.900 at 25/25°C	Spitz, 1979
Flash point: (Tag open cup)	85°C	Spitz, 1979
Vapor pressure:	0.23 mm Hg at 20°C	Weber et al., 1981
Vapor density: (air = 1.0)	4.01	Verschueren, 1983
Conversion factors:	1 mg/m ³ = 0.210 ppm 1 ppm = 4.75 mg/m ³	Verschueren, 1983
Water solubility:	freely soluble 10 ⁶ ppm at 25°C	Hann and Jensen, 1977; U.S. EPA-NIH, 1984
pK _a at 25°C:	9.83-10.93	Perrin, 1964

Aliphatic polyamines, such as hexamethylenediamine, undergo reactions typical of compounds containing primary and secondary amines (Spitz, 1979). For example, they react readily with inorganic acids to form salts, and they react with the alkylene oxides.

1.3. PRODUCTION DATA

Hexamethylenediamine is manufactured on a commercial scale by the hydrogenation of adiponitrile (Lowenheim and Moran, 1975). Hydrogen, adiponitrile and ammonia are fed to a converter where the reaction takes place; the reactor products and non-reactants are then separated by fractionation. The current United States manufacturers of hexamethylenediamine are as follows (SRI, 1984):

		Annual Capacity (Millions of Pounds)
DuPont	Orange, TX	475
	Victoria, TX	315
Monsanto	Decatur, AL	200
	Pensacola, FL	<u>200</u>
Total		1190

The last year for which the U.S. International Trade Commission reported production volumes for hexamethylenediamine is 1976, when domestic production was 856 million pounds (USITC, 1977). As noted above, current industry capacity is 1.19 billion pounds annually.

1.4. USE

Hexamethylenediamine is used as a basic intermediate in the production of nylon 6,6 and nylon 6,9, and in 6,10 and 6,12 resins. It is also used to make hexamethylenediisocyanate for use in polyurethane production, and as an intermediate to produce wet strength resins, boiler feedwater additives and polyamide adhesives (Kuney, 1983).

Nylon 6,6 is manufactured by the condensation reaction between hexamethylenediamine and adipic acid. Nylon 6,9 and 6,12 use azelaic acid and dodecanedioic acid, respectively, instead of adipic acid. These plastics are used in a wide variety of applications including injection moldings, extruded plastics, and film and wire coating purposes. In 1978, sales of nylon 6,6 reached ~180 million pounds in the United States alone (Welgos, 1982).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The fate of hexamethylenediamine in water will depend on its ability to undergo biological, chemical and photochemical reactions, and partitioning (transport) from the water column into air or sediment. According to the available literature, hexamethylenediamine biodegrades significantly in natural systems. Using the MITI test, both Kawasaki (1980) and Sasaki (1978) found hexamethylenediamine to be readily biodegradable; neither author listed specific degradation rates for hexamethylenediamine. Zahn and Wellens (1980) found that hexamethylenediamine was degraded rapidly in a batch water system with activated sludge (1 g/l TS; 1000 mg/l COD). Greater than 90% of the hexamethylenediamine was degraded in 6 days, with 3 days acclimation and a COD/day consumption rate of 26%. Zahn and Huber (1975) determined that 91% of the original hexamethylenediamine present in two natural water system tests was degraded in 10.8 days. The first test used the Zahn-Wellens COD method (14 days), while the second test used the modified OECD method (10 days acclimation and 19-day test). Grula and Grula (1976) found that thermophilic bacteria decomposed hexamethylenediamine in deep disposal wells under conditions of 50-70°C and 100 atmospheres pressure. A number of Russian studies have shown that Bacillus subtilis and cell-free extracts from the microorganism are effective in removing hexamethylenediamine from wastewaters (Gvozdyak et al., 1980; Roi, 1977; Garbara and Rotmistrov, 1982; Vasilenskaya et al., 1980; Nikonenko et al., 1981). Also, Kuchinskii et al. (1977) found that biological treatment of plant wastewater (in the Soviet Union, no treatment conditions are available) were effective in completely oxidizing hexamethylenediamine.

Pertinent data regarding the chemical hydrolysis or photodecomposition of hexamethylenediamine in water were not located in the available literature as cited in the Appendix. The chemical structure of hexamethylenediamine suggests that hydrolysis under environmental conditions is not likely to be important, especially in relation to biodegradability.

The transport of hexamethylenediamine in the aquatic environment will depend on the ability of the compound to volatilize, to adsorb to particulate organic matter or to bioaccumulate in aquatic organisms. Specific experimental data for these transport mechanisms were not available; however, the extremely high water solubility of hexamethylenediamine suggests that adsorption and bioaccumulation are not important. Also, the water solubility and vapor pressure suggests that volatilization is unlikely to be important.

2.2. AIR

Pertinent data regarding the fate or transport of hexamethylenediamine in the atmosphere were not located in the available literature as cited in the Appendix. Without additional experimental data, it is difficult to predict the importance of various chemical or physical removal processes.

2.3. SOIL

Ennis (1975) showed that soil isolates of various fungi and bacteria (Aspergillus, Alcaligenes, Flavobacterium) were effective in degrading hexamethylenediamine. The degradation (oxidation) was found to be an adaptive or inducible process. In addition, the data presented in Section 2.1. have shown that hexamethylenediamine can be biodegraded readily. Therefore, the microbial decomposition of hexamethylenediamine in the soil is likely to be environmentally significant. It is also likely that microbial decomposition is the predominant pathway by which hexamethylenediamine is chemically altered in the soil.

Pertinent data regarding the hydrolysis or photolysis of hexamethylenediamine in the soil were not located in the available literature as cited in the Appendix. Photolysis, whether direct or photosensitized, would only occur at the soil surface.

The transport mechanisms, adsorption and volatilization, have not been studied in regard to hexamethylenediamine. The high water solubility predicts that hexamethylenediamine is highly mobile in soil and, therefore, easily leached. This mobility would limit potential photolysis at the soil surface in moist soils.

3. EXPOSURE

3.1. WATER

Pertinent data regarding environmental exposure to hexamethylenediamine in water were not located in the available literature as cited in the Appendix. The U.S. EPA STORET Data Base reports no listings for hexamethylenediamine.

3.2. FOOD

Pertinent data regarding exposure to hexamethylenediamine in food were not located in the available literature as cited in the Appendix.

3.3. INHALATION

Pertinent data regarding exposure to hexamethylenediamine in the air were not located in the available literature as cited in the Appendix.

3.4. DERMAL

Pertinent data regarding exposure to hexamethylenediamine on the skin were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Male F344 rats treated by gavage with 1,6- ^{14}C -hexamethylenediamine in water or saline at a dose of 0.4 mg/kg bw excreted 47% of the administered radioactivity in the urine, 20% in the expired air as $^{14}\text{CO}_2$ and 27% in feces over a 72-hour period (David and Heck, 1983). The results indicate that at least 67% of the administered radioactivity was absorbed from the GI tract. It is unknown what percentage, if any, of the fecal radioactivity was due to biliary excretion.

Kusche et al. (1975) tested the ability of the small intestine to inactivate hexamethylenediamine by oxidative deamination in vitro. Hexamethylenediamine was a good substrate for highly purified preparations of amine oxidases isolated from dog small intestine. The results suggest that deamination may occur prior to uptake into the systemic circulation, if the enzymes are available for attack in vivo.

4.2. DISTRIBUTION

The tissue levels of radioactivity (nmol equivalents/g tissue or fluid $\pm$ SE) 72 hours after treatment of male rats with a gavage dose of 0.4 mg ^{14}C -hexamethylenediamine/kg bw were as follows: prostate, 250 $\pm$ 30; intestine, 113 $\pm$ 8; kidney, 194 $\pm$ 27; liver, 171 $\pm$ 26; spleen, 82 $\pm$ 13; testes, 64 $\pm$ 8; lungs, 77 $\pm$ 11; heart, 51 $\pm$ 8; brain, 25 $\pm$ 6; and blood, 31 $\pm$ 5 (David and Heck, 1983).

David and Heck (1983) also studied the tissue distribution of radioactivity in male and female F344 rats following i.v. injection of 100 μCi of ^{14}C -hexamethylenediamine using whole-body autoradiography. In a male rat killed 1 hour after injection, the greatest amount of radioactivity was found in the intestine, followed by the liver and kidney. Radioactivity was

also present in the bladder, thymus, salivary glands and prostate gland, but to a lesser extent than in the liver. Little radioactivity was observed in brain or testes after 1 hour. In a male rat killed 24 hours after injection of ^{14}C -hexamethylenediamine, the highest concentration of radioactivity was found in the prostate, followed by the intestine and liver. Therefore, the radioactivity from ^{14}C -hexamethylenediamine accumulated and persisted in the prostate of male rats. For the female rats, a high concentration of radioactivity was present in the uterus after 1 hour but not after 24 hours. Little radioactivity was present in the ovary at 1 hour or 24 hours after injection. The distribution in other tissues of the female rats was not reported.

4.3. METABOLISM

David and Heck (1983) found that male rats treated by gavage with ^{14}C -hexamethylenediamine excreted 20% of the radioactivity as $^{14}\text{CO}_2$ in 72 hours. Analysis of the 72-hour urinary radioactivity (47% of the administered dose) indicated that 30% of the urinary radioactivity was unchanged hexamethylenediamine. Further characterization of metabolites was not reported.

As indicated in Section 4.1., the ability of hexamethylenediamine to act as a substrate for intestinal amine oxidases in vitro indicates that deamination may occur in tissues containing the enzymes (Kusche et al., 1975).

4.4. EXCRETION

As discussed in Section 4.1., rats treated orally with ^{14}C -hexamethylenediamine excreted 47% of the administered radioactivity in the urine, 27% in the feces and 20% as $^{14}\text{CO}_2$ in 72 hours (David and Heck, 1983). The amount and pattern of excretion of radioactivity over shorter periods of time following treatment were not reported.

5. EFFECTS

5.1. CARCINOGENICITY

No carcinogenicity studies of hexamethylenediamine were located in the available literature as cited in the Appendix. IARC (1979) indicated that hexamethylenediamine was considered by the Working Groups, but the lack of adequate data precluded the preparation of a monograph. This chemical has been approved for testing by the National Toxicology Program but, as of July, 1984, has not been assigned to a laboratory (NTP, 1984).

5.2. MUTAGENICITY

No mutagenicity studies of hexamethylenediamine, per se, were located in the available literature as cited in the Appendix. Thomas et al. (1979) reported that the addition of hexamethylenediamine (0.2 mM) to the assay system resulted in 1.5-fold enhancement of the NaNO_2 -induced (100 mM) rate of mutation in native DNA isolated from Hemophilus influenzae to give erythromycin-resistant mutants following transformation in H. influenzae cells. It was presumed that the reaction of hexamethylenediamine with NaNO_2 resulted in the formation of the N-nitroso derivative. Murphey-Corb et al. (1983) found that the reaction mixture of hexamethylenediamine (944 mM) and NaNO_2 (3.15 mM) did not increase the rate of reverse mutation in Salmonella typhimurium strains TA1950, TS24, TA1537, TA1538, TA1952 and G46 induced by nitrite alone. The mixture was tested by liquid incubation at six serial 2-fold dilutions of the stock solution.

5.3. TERATOGENICITY

David and Heck (1983) administered hexamethylenediamine-HCl to groups of 13 or 14 pregnant F344 rats at gavage doses of 0, 10, 100 or 200 mg/kg bw/day from days 0-15 of gestation, at which time they were killed. The basis for establishing day 0 of gestation was not defined. The investi-

gators stated that the weight gain of dams treated at 200 mg/kg bw/day was significantly lower than that of controls, but no data were presented. The only reproductive parameters examined were the mean number of corpora lutea, the mean litter size and the total number of resorptions. There were no significant differences between treated groups and controls in any of these parameters. The study was designed to determine if hexamethylenediamine, an inhibitor of ovarian ornithine decarboxylase activity (Section 5.4.), had an early effect on gestation.

In another study regarding the role of ornithine decarboxylase activity in mammalian embryogenesis, Manen et al. (1983) administered hexamethylenediamine in 0.9% saline i.p. at doses of 0 or 0.89 mmol/kg bw (~103 mg/kg bw) to pregnant CD-1 mice. The mice were treated with the dose 4 times at 3-hour intervals on day 10, 11, 12, 13 or 14 of gestation, the days of peak fetal ornithine decarboxylase activity. Day 1 of gestation was defined as the day of vaginal plug formation. All dams were sacrificed on day 18 of gestation. The results of the fetal examination are presented in Table 5-1. Hexamethylenediamine treatment on any gestational day had no significant effect on the percentage of resorbed or dead fetuses. Fetal weights were significantly ($p < 0.05$) reduced when the chemical was administered on days 10, 11 or 12. Only when mice were treated on day 10 was there a statistically significant increase in the incidence of unossified supraoccipitals, although the increased incidence for treatment day 13 was appreciable. Hexamethylenediamine treatment had no effect on the incidence of abnormal ribs.

TABLE 5-1
Effect of Hexamethylenediamine on Mouse Development^a

Treatment Day	Treatment ^b Group	Litters Examined	Mean Fetal Weight (g $\pm$ SE)	Number Resorbed or Dead/ Total Number of Fetuses (%)	Abnormal Ribs (%)	Unossified Supraoccipital (%)
10	control	15	1.03 $\pm$ 0.04	21/99 (10.6)	0	10.4
		17	0.86 $\pm$ 0.04 ^c	28/218 (12.8)	0	43.8 ^c
11	control	17	1.03 $\pm$ 0.03	36/213 (16.9)	0	6.3
		16	0.89 $\pm$ 0.04 ^c	25/196 (12.8)	0	12.4
12	control	15	1.00 $\pm$ 0.03	18/204 (8.8)	0	0
		17	0.87 $\pm$ 0.02 ^c	20/224 (8.9)	0	8.4
13	control	18	0.97 $\pm$ 0.05	54/239 (22.5)	0	17.4
		20	0.84 $\pm$ 0.04	58/238 (24.4)	0	42.6
14	control	16	0.97 $\pm$ 0.03	41/201 (20.4)	0	11.7
		18	1.02 $\pm$ 0.02	20/213 (9.4)	0	4.9

^aSource: Manen et al., 1983

^bThe mice were treated intraperitoneally with 4x0.89 mmol/kg bw in 0.9% saline at 3-hour intervals on the day indicated. Controls received intraperitoneal injections of saline.

^cSignificantly different from control (p<0.05)

5.4. OTHER REPRODUCTIVE EFFECTS

Guha and Janne (1977) reported that i.p. injection of prepubertal female Wistar or Sprague-Dawley rats with hexamethylenediamine (125 μ mol/100 g bw) resulted in complete inhibition of the stimulation of ovarian ornithine decarboxylase by HCG. The inhibition of ornithine decarboxylase was accompanied by the partial inhibition of the progesterone accumulation stimulated by HCG. These results suggest that nonphysiologic diamines may interfere with the normal regulatory processes of ovulation.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The only information available on the effects of long-term exposure to hexamethylenediamine was in abstracts of studies from the Russian literature. Two abstracts reported that rats, mice and rabbits receiving hexamethylenediamine in the drinking water (concentrations not reported) for 1-2 years had hyperplasia of spleen lymphoid tissue, enhanced plasmocytogenesis, hyperplasia of extramedullar hematopoiesis and induction of autoimmune responses (Ponomoreva and Merkushev, 1978; Shubik et al., 1976). Further details were not reported.

In two other abstracts, it was reported that groups of 15 female white rats were exposed continuously to hexamethylenediamine in air at concentrations of 0, 0.001, 0.04 or 1 mg/m³ for 3 months (Kulakov, 1965, 1967). Observations in rats exposed to 1 mg/m³ included hematologic changes, "disturbed motor responses and pathological changes of inner organs." Exposure to 0.04 mg/m³ reportedly resulted in similar changes of a lesser degree, reduction in body weight, increased white blood cell count, decreased phagocytic activity and a rise in V1 antibody titer. No effects were observed at 0.001 mg/m³.

In an abstract of a study by Izraellet and Laivina (1980), chronic (duration not specified) exposure of rats to hexamethylenediamine in air at 1 mg/m³ was reported to result in leukocytolysis and lethargy.

5.6. OTHER RELEVANT INFORMATION

Vernot et al. (1977) reported the acute oral LD₅₀ of hexamethylenediamine to be 800 mg/kg with 95% confidence limits of 470-1360 mg/kg for male rats, and 750 mg/kg with 95% confidence limits of 510-1100 mg/kg for female rats. The acute dermal LD₅₀ for rabbits was 1100 mg/kg with 95% confidence limits of 600-2120 mg/kg. Hexamethylenediamine was irritating to the skin of guinea pigs, but produced no sensitization (Zeller, 1957).

Inhalation exposure to hexamethylenediamine of four male and four female rats at 10 mg/l (10,000 mg/m³), 6 hours/day for 2 days resulted in nasal irritation, labored respiration, lethargy and death of one rat of each sex (Gage, 1970). Autopsy and histologic examination revealed lung congestion, peribronchiolar inflammation, hemorrhage and edema of lungs, and vacuolization of renal tubules. Inhalations of 5 mg/l (5000 mg/m³), 6 hours/day for 11 days resulted in nose and lung irritation, reduced body weight gain, lethargy, unthriftiness and one death. No signs of toxicity were observed at inhalation concentrations of 1 mg/l (1000 mg/m³), 6 hours/day for 15 days.

Hexamethylaminediamine has been widely studied for its regulatory role in tissue growth and biosynthesis. Among the effects attributed to this diamine are: stimulation of the synthesis of polyphenylalanine in the Escherichia coli cell free system, stimulation of globin m-RNA-dependent polypeptide synthesis in a wheat germ cell free system, and stimulation of the breakdown of poly C by bovine pancreatic RNAase A (Igarashi et al., 1980); induction of differentiation in murine erythroleukemia cells in vitro

(Reuben et al., 1976); inhibition of neuroblastoma replication and ornithine decarboxylase activity in vitro (Chapman and Glant, 1980); inhibition of ornithine decarboxylase in Ehrlich ascites tumors in mice in vivo (Kallio et al., 1977); prevention of the increase in ornithine decarboxylase activity induced by serum in mouse 3T3 fibroblasts or SV-40 transformed 3T3 cell lines (Bethell and Pegg, 1979); inhibition of uptake of putrescine by rat prostate-derived tumor cells (Heston et al., 1984); inhibition of uptake of putrescine by rat lung slices (Gordonsmith et al., 1983); and inhibition of phospholipase C from human platelets (Nahas and Graff, 1982).

6. AQUATIC TOXICITY

6.1. ACUTE

Pertinent data regarding the acute toxicity to aquatic life of hexamethylenediamine were not located in the available literature as cited in the Appendix.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity to aquatic life of hexamethylenediamine were not located in the available literature as cited in the Appendix.

6.3. PLANT EFFECTS

Pertinent data regarding the effects to aquatic plants of hexamethylenediamine were not located in the available literature as cited in the Appendix.

6.4. RESIDUE

Pertinent data regarding residues of hexamethylenediamine were not located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

Pertinent data regarding existing guidelines and standards for hexamethylenediamine were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

No studies testing the carcinogenicity of hexamethylenediamine were located in the available literature as cited in the Appendix. No studies testing the mutagenicity of hexamethylenediamine, per se, were located; however, the product of the reaction of hexamethylenediamine and NaNO_2 had a greater mutagenic effect than did nitrous acid alone in H. influenzae DNA (Thomas et al., 1979), but not in six tester strains of S. typhimurium (Murfhey-Corb et al., 1983). There were no effects on reproductive parameters (number of corpora lutea, litter size or number of resorptions) in pregnant rats treated orally with hexamethylenediamine at doses <200 mg/kg bw/day during gestation, although maternal weight gain was reduced at the highest dose (David and Heck, 1983). Fetal body weights were reduced when hexamethylenediamine at 0.89 mmol/kg bw was administered i.p. to pregnant mice four times on day 10, 11 or 12 of gestation, and the incidence of unossified supraoccipitals was increased in fetuses of mice treated on day 10 (Manen et al., 1983).

The only available data regarding long-term exposure to hexamethylenediamine were abstracts of studies from the Russian literature. In a study of 1-2 years duration, rats, mice and rabbits receiving hexamethylenediamine in their drinking water had hyperplasia of spleen lymphoid tissue and enhanced hematopoiesis (Ponomareva and Merkushev, 1978; Shubik et al., 1976), but no concentrations or other details were provided. Therefore, the study is unsuitable for risk assessment. Several studies from the Russian literature reported effects of hematologic changes, immunologic and motor response disturbances and unspecified internal pathologic changes in rats exposed for 3 months to inhalation concentrations of hexamethylenediamine of

0.04-1 mg/m³, with no effects observed at 0.001 mg/m³ (Kulakov, 1965, 1967; Izraellet and Laivina, 1980). The abstracts of these inhalation studies provided limited detail. Furthermore, the studies were too short in duration without substantiation from chronic studies for derivation of an ADI.

9. REPORTABLE QUANTITY RANKING BASED ON CHRONIC TOXICITY

The only information regarding the effects of long-term exposure of animals to hexamethylenediamine was available in abstracts of studies from the Russian literature. It was reported in two abstracts of studies by Ponomareva and Merkushev (1978) and Shubik et al. (1976) that rats, mice and rabbits receiving hexamethylenediamine in the drinking water at unspecified concentrations for 1-2 years had hyperplasia of spleen lymphoid tissue, enhanced plasmocytogenesis, and hyperplasia of extramedullar hematopoiesis. Inhalation exposure of rats to hexamethylenediamine in air at 0.04-1 mg/m³ for 3 months was reported to result in hematologic changes, disturbed motor responses, unspecified internal pathology, reduced body weight and immunologic changes (Kulakov, 1965, 1967; Izraellet and Laivina, 1980). The lack of experimental detail in the drinking water exposure study, the lack of sufficient description of effects and the limited duration of the inhalation studies preclude the derivation of an RQ (Table 9-1).

TABLE 9-1

Hexamethylenediamine

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:

Dose

Effect:

Reference:

RV_d

RV_e:

Composite Score:

RQ: Data are insufficient to derive an RQ.

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in July, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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